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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,068	01/08/2004	Bao-Lu Chen	PP-17853-005	6547

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EXAMINER

ROOKE, AGNES BEATA

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/753,068

Applicant(s)

CHEN ET AL.

Examiner

Agnes B Rooke

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 01 March 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-5 and 7-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 7-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)                                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This final action is in response to the Applicant's reply filed on March 1, 2005.

Claims 1-5 and 7-32 are pending. Claim 6 has been cancelled.

The amendments to the claims filed on March 1, 2005 have been acknowledged.

The priority is claimed to 60/438,519, filed on 01/08/2003.

### **Rejections Withdrawn**

#### **35 U.S.C. 112 second paragraph**

Examiner withdraws the rejection of Claim 1 under 35 U.S.C. 112 second paragraph as to the spelling of the name of TFPI, since Applicant appropriately amended the claim.

Examiner withdraws the rejection of Claims 2 and 3, since the phrase "about 70% or more homologous to TFPI (SEQ ID NO:1) is definite, since examiner can interpret the phrase of "about 70% or more" as being the range of 65% to 100%.

Examiner withdraws the rejection of Claims 8 and 9 regarding the phrase "enriched" since adequate support was pointed out by the Applicant in paragraph 43 of the specification.

#### **35 U.S.C. 103(a)**

Examiner withdraws the rejection of Claims 1-5 and 7-32 under 35 U.S.C. 103(a) as unpatentable over Petereson et al. (US 2002/0092627).

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Examiner stated that Petersen et al. teach a pharmaceutical composition consisting of factor VII and factor XII, and/or stabilizer, and/or detergent, and/or a neutral salt, and/or an antioxidant, and/or a preservative, and/or a protease inhibitor, and/or TFPI inhibitor, and where Petersen et al. did not teach a single composition comprising TFPI variants and antioxidants in a pharmaceutical composition.

Applicant responded that Petersen et al. does not teach or suggest any type of composition comprising TFPI or a TFPI variant, and only disclosed TFPI-inhibitor in composition, and therefore the reference does not teach or suggest the instant invention.

Examiner agrees and recognizes that Petersen et al. teach TFPI-inhibitor and not TFPI or TFPI variants and therefore the rejection of Claims 1-5 and 7-32 is withdrawn.

**Rejections Maintained**

**35 U.S.C. first paragraph**

**Written Description**

Examiner maintains the rejection of Claims 1-5 and 7-32 under 35 U.S.C. first paragraph.

Examiner in the first office action stated that TFPI variants that include analogs and derivatives, as well as fragments of TFPI do not satisfy the written description requirement, and that the word "include" is an open-ended phrase and therefore encompasses all possible variants of TFPI.

Applicant responded that the present specification explicitly describes numerous representative species of TFPI variants, which fall within recited genus and cited paragraphs 26-29 to support the argument. Also, Applicant states that the office action cites no basis for concluding that this specification does not provide a representative number of species within the genera of TFPI variants.

Examiner disagrees, because TFPI variants include analogs and derivatives that it could be anything, and represent an infinite number of proteins, and for example, any protein that contains alanine can be considered TFPI variants. Also, there is no such thing as representative number of infinity.

Therefore, the claims as amended at the present time do not satisfy the written description requirement as to the TFPI variants.

### **Enablement**

Examiner maintains the rejection of Claims 1-5 and 7-32 under 35 U.S.C. 112 first paragraph.

#### **1. Breadth of the claims and nature of the invention**

Examiner stated that the claims are broad and encompass unspecified TFPI variants and that there could be many variants that are about 70% or more homologous to the TFPI.

Applicant responded that the specification explicitly describes numerous representative species of TFPI variants, which fall within the recite genus.

Examiner disagrees because the number of TFPI variants is infinite, and the Applicant did not describe in the specification an infinite amount of the variants.

2. Working examples, state of the art, and relative skill in the art

Examiner stated that specification indicated Ala-TFPI as variant, and that working examples 2-8 used only Ala-TFPI in their experiments, and no other variants were included in the experiments. Further, examiner stated that even though the relative skill in the art is high, the general knowledge and level of the skill in the art do not supplement the omitted description of other TFPI variants that Applicant tries to claim.

Applicant responded that the working examples for other TFPI variants are not required, and that specification addressed to those skilled in the art, and that the skill in the art is high.

Examiner stands by the rejection because the working examples refer only to one variant, Ala-TFPI, and the number of potential other TFPI variants is infinite.

3. Predictability of the art

Examiner stated that claims encompass unidentified number of TFPI variants, therefore the function of the variants is unpredictable since the potential variants of TFPI are unascertained. Therefore, the Applicant is not enabled for the variants due to the unpredictability in the art because Applicants do not know the effects of structural alterations of all TFPI variants.

4. Guidance provide in the specification and quantity of experimentation required

Examiner stated that there is an infinite number of TFPI variants and therefore an infinite number of experimentation and testing that is necessary.

Applicant responded that the specification provides descriptions of TFPI variants, solubilizing agents, antioxidants and how to make the composition, and that the administration of compositions comprising TFPI variants is well known in the art.

Examiner responds that because the structure of all TFPI variants claimed is unascertainable the function of all the variants cannot be predicted and, thus the appropriate testing must be performed, even though the compositions comprising TFPI variants are known in the art. Further, the working examples do not demonstrate the claimed TFPI variants, and the teaching in the specification is limited. In the office action examiner asked the Applicant that the listing of specific TFPI variants claimed be provided because the TFPI variant is not limited in scope in anything. Should Applicant limit the TFPI variants to less than infinite number that would be a step in a limiting the scope of the claims.

**35 U.S.C. 112 second paragraph**

Examiner maintains the rejection of Claims 1 and 7 under the 35 U.S.C. 112 second paragraph.

Examiner rejected the claims because they refer to TFPI variants where examiner stated that metes and bounds of the term TFPI variant is not clear and too

broad, and thus specific examples of TFPI variants claimed must be provided, since structural variants have distinct biological and functional features.

Applicant referred to the discussion in connection of the written description when responding to the rejection regarding TFPI variant.

Examiner maintains the rejection of Claims 1 and 7 since the structure of all TFPI variants is unascertainable, and the number of combinations is indefinite, and therefore the rejection is maintained.

**35 U.S.C. 103(a)**

Examiner maintains the rejection of Claims 1-5 and 7-32 under 35 U.S.C. 103(a) as unpatentable over **Chen et al.** (U.S. 6,525,102) in view of **Kosoglou et al.** (U.S. 2002/0147184 A1).

Examiner stated that **Chen et al.** (U.S. 6,525,102) teach a stabilized liquid pharmaceutical composition comprising tissue factor pathway inhibitor (TFPI) or variant thereof, a stabilizing agent, a buffering agent, wherein the stabilizing agent is arginine in its free base form and the buffering agent is succinic acid. See Claims 6-12, 21-24. These teachings meet the limitations of the instant claims, directed to the stabilized pharmaceutical compositions of TFPI, TFPI variant, a stabilizing agent, such as arginine, a buffering agent, and a succinic acid. **Chen et al.** (U.S. 6,525,102) lack an antioxidant. See page 12.



**Kosoglou et al.** (U.S. 2002/0147184 A1) teaches compositions, therapeutic combinations and different methods useful in treating vascular conditions and lowering plasma levels sterols. See page 1, paragraph 1. Above all, the aforementioned compositions comprise tissue factor pathway inhibitor (TFPI) and at least one antioxidant. See Claims 27 and 42. Claim 27, teaches composition wherein the factor Xa inhibitor is selected from the group consisting of tissue factor pathway inhibitor (TFPI), and Claim 42 teaches that the composition further comprises at least one antioxidant. Claims 27 and 42 teach TFPI and an antioxidant in one composition. Furthermore, teachings of **Kosoglou et al.** (U.S. 2002/0147184 A1) are analogous with the instant invention, since in both instances, TFPI and an antioxidant are present in one composition. However, the reference does not teach TFPI variants and an antioxidant in one composition.

Applicant responded that **Chen et al.** teach removal of oxygen by nitrogen purging and degassing, but only in compositions comprising IL-2 (Example 2), and that the reference does not teach that the method would be useful in a composition comprising TFPI and its variants. Further, Applicant stated that the reference does not teach oxygen displacement gases.

Examiner disagrees and maintains the rejection because **Chen et al.** and **Kosoglou et al.** suggest a composition, which contains all the elements, including TFPI. Also, oxygen removal by nitrogen purging and degassing is a common method to

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reduce photodecomposition and air oxidation and to increase stabilization for optimal storage stability of a protein. Therefore, it would have been obvious to use the same method in a composition containing TFPI.

Therefore the rejection is maintained as to Claims 1-5 and 7-32.

A person of ordinary skill in the art at the time the invention was made would have been motivated to combine teachings of Chen et al. (U.S. 6,525,102) and Kosoglou *et al.* (U.S. 2002/0147184 A1) because of the need to have a protein, such as TFPI, in a stable form to retain its bioactivity. In both cases, stabilizing agent and an antioxidant was added to a composition to stabilize TFPI.

Examiner maintains the rejection of Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Chen et al.** (U.S. 6,525,102) in view of **Kosoglou et al.** (U.S. 2002/0147184 A1) taken further with **Takruri** (U.S. 5,272,135).

Takruri (U.S. 5,272,135) teaches stabilizing formulations for methionine containing polypeptides by addition of methionine to inhibit oxidation of the methionine residue(s). Column 2, line 60-68. The added methionine stabilizes the preparation containing a polypeptide by inhibiting the rapid oxidation of the methionine residue(s) to methionine sulfoxide. Column 2, line 60-68.

Applicant responded with an amendment to Claim 10, by adding the phrase "further comprises" and therefore overcomes the rejection of Claims 14 and 15.

Examiner disagrees and maintains the rejection because a person of ordinary skill in the art at the time the invention was made would have been motivated to substitute methionine as the antioxidant with TFPI in the composition of Chen *et al.* (U.S. 6,525,102), because Takruri (U.S. 5,272,135) establishes methionine would act as an antioxidant and improve stability by reducing the oxidation of a polypeptide chain.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use methionine as antioxidant in a composition containing TFPI or its variants.

Examiner maintains the rejection of Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Chen *et al.*** (U.S. 6,525,102). Chen *et al.* teach that addition of oxygen removal by nitrogen purging and degassing decreases the percentage of the methionine oxidative species and improves protein stability. See Example 2. However, the reference does not teach oxygen removal in a composition containing TFPI or TFPI variants.

Applicant responded that Chen *et al.* do not teach or suggest a composition comprising TFPI or its variants and an oxygen displacement gas.

Examiner disagrees and maintains the rejection because oxygen displacement gas is a common method and it is proven to prevent oxidation of methionine in a protein

(See Example 2) and thus would prevent oxidation of TFPI and thus it would increase the TFPI composition stability.

A person of ordinary skill in the art at the time the invention was made would have been motivated to remove oxygen from the composition of TFPI because the procedure would reduce the percentage of the methionine oxidative species, and thus improve the stability of TFPI in a composition.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to design a stabilized pharmaceutical composition comprising TFPI, and an antioxidant, such as an oxygen displacement gas.

### ***Conclusion***

No Claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

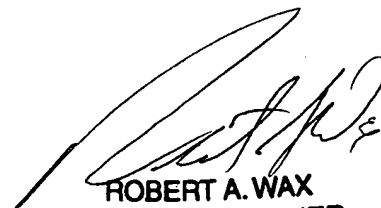
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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-273-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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PRIMARY EXAMINER  
Art Unit 1653